CLAIMS

What is claimed is:

1. A method of modulating the activity of a melanocortin receptor, said method comprising contacting said receptor with a peptide having the formula:

$CX^1X^2X^3X^4X^5X^6CX^7X^8X^9X^{10}X^{11}X^{12}CCDPX^{13}ATCYCX^{14}X^{15}X^{16}NAFCYCR_n$

wherein

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, and X^{16} are independently selected amino acids, and

n is zero or one.

2. The method of claim 1, wherein X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, and X^{16} are independently selected from the group consisting of alanine, asparagine, arginine,aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.

3. The method of claim 1, wherein said peptide is not CVRLHESCLGQQVPCCDPAATCYCRFFNAFCYC (SEQ ID NO:3).

4. The method of claim 1, wherein $X^1X^2X^3X^4X^5X^6$ is VRLHES or conservative substitutions thereof.

5. The method of claim 4, wherein $X^1X^2X^3X^4X^5X^6$ is VRLHES.

6. The method of claim 1, wherein $X^7X^8X^9X^{10}X^{11}X^{12}$ is LGQQVP or conservative substitutions thereof.

7. The method of claim 6, wherein $X^7X^8X^9X^{10}X^{11}X^{12}$ is LGQQVP.

8. The method of claim 7, wherein $X^7X^8X^9X^{10}X^{11}X^{12}$ is LGQQVP or conservative substitutions thereof.

9. The method of claim 8, wherein $X^7X^8X^9X^{10}X^{11}X^{12}$ is LGQQVP.

10. The method of claim 1, wherein X^{13} is not a cysteine.

11. The method of claim 1, wherein X^{13} is A.

12. The method of claim 1, wherein $X^{14}X^{15}X^{16}$ is RFF or conservative substitutions thereof.

13. The method of claim 4, wherein $X^{14}X^{15}X^{16}$ is RFF or conservative substitutions thereof.

14. The method of claim 8, wherein $X^{14}X^{15}X^{16}$ is RFF or conservative substitutions thereof.

15. The method of claim 1, wherein said receptor is in a cell culture.

16. The method of claim 1, wherein said receptor is *in vivo* culture.

17. The method of claim 1, wherein said receptor is an MC3 receptor.

18. The method of claim 1, wherein said receptor is an MC4 receptor.

19. A library for screening for modulators of a melanocortin receptor, said library comprising a plurality of polypeptide members wherein said members have the formula:

$$CX^1X^2X^3X^4X^5X^6CX^7X^8X^9X^{10}X^{11}X^{12}CCDPX^{13}ATCYCX^{14}X^{15}X^{16}NAFCYCR_n$$

wherein

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, and X^{16} are independently selected amino acids, and

n is zero or one.

20. The library of claim 19, wherein X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, and X^{16} are independently selected from the group consisting of aspartic acid, alanine, asparagine, arginine,cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine.

21. The method of claim 19, wherein $X^1X^2X^3X^4X^5X^6$ is VRLHES or conservative substitutions thereof.

22. The method of claim 21, wherein $X^1X^2X^3X^4X^5X^6$ is VRLHES.

23. The method of claim 19, wherein $X^7X^8X^9X^{10}X^{11}X^{12}$ is LGQQVP or conservative substitutions thereof.

24. The method of claim 23, wherein $X^7X^8X^9X^{10}X^{11}X^{12}$ is LGQQVP.

25. The method of claim 24, wherein $X^7X^8X^9X^{10}X^{11}X^{12}$ is LGQQVP or conservative substitutions thereof.

26. The method of claim 25, wherein $X^7X^8X^9X^{10}X^{11}X^{12}$ is LGQQVP.

27. The method of claim 19, wherein X^{13} is not a cysteine.

28. The method of claim 19, wherein X^{13} is A.

29. The method of claim 19, wherein $X^{14}X^{15}X^{16}$ is RFF or conservative substitutions thereof.

30. The method of claim 21, wherein $X^{14}X^{15}X^{16}$ is RFF or conservative substitutions thereof.

31. The method of claim 25, wherein $X^{14}X^{15}X^{16}$ is RFF or conservative substitutions thereof.

32. A method of prescreening for a modulator of a melanocortin receptor, said method comprising:

i) contacting a melanocortin receptor a peptide having the formula:

$$CX^1X^2X^3X^4X^5X^6CX^7X^8X^9X^{10}X^{11}X^{12}CCDPX^{13}ATCYCX^{14}X^{15}X^{16}NAFCYCR_n$$

wherein

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, and X^{16} are independently selected amino acids, and

n is zero or one; and

ii) detecting binding of said peptide to said melanocortin receptor wherein specific binding of said peptide to said melanocortin receptor indicates that said peptide is a potential modulator of said melanocortin receptor.

33. The method of claim 32, wherein said peptide is not CVRLHESCLGQQVPCCDPAATCYCRFFNAFCYC (SEQ ID NO:3).

34. The method of claim 32, wherein said melanocortin receptor is selected from the group consisting of MC3r, and MC4r.

35. A method of screening for a modulator of melanocortin receptor activity, said method comprising:

i) contacting a melanocortin receptor with a peptide having the formula:

$CX^1X^2X^3X^4X^5X^6CX^7X^8X^9X^{10}X^{11}X^{12}CCDPX^{13}ATCYCX^{14}X^{15}X^{16}NAFCYCR_n$

wherein

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, and X^{16} are independently selected amino acids, and

n is zero or one; and

ii) detecting activity of said melanocortin receptor wherein a difference in activity of said receptor, as compared to a control, indicates that said peptide is a modulator of melanocortin receptor activity.

36. The method of claim 35, wherein said control is a negative control comprising the same assay without said peptide.

37. The method of claim 35, wherein said peptide is not CVRLHESCLGQQVPCCDPAATCYCRFFNAFCYC (SEQ ID NO:3).

38. The method of claim 35, wherein said melanocortin receptor is selected from the group consisting of MC3r, and MC4r.

39. A polypeptide comprising a peptide sequence having the formula 35wherein said polypeptide is not AGRP and said polypeptide is not MARP.

40. The polypeptide of claim 39, wherein said polypeptide excludes one or more of the final 13 residues of MARP (residues 34-46 of MARP).

41. The polypeptide of claim 39, wherein said polyypeptide has the formula:

$CX^1X^2X^3X^4X^5X^6CX^7X^8X^9X^{10}X^{11}X^{12}CCDPX^{13}ATCYCX^{14}X^{15}X^{16}NAFCYCR_n$

wherein

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, and X^{16} are independently selected amino acids, and

n is zero or one.

42. The polypeptide of claim 41, wherein said polypeptide is not CVRLHESCLGQQVPCCDPAATCYCRFFNAFCYC (SEQ ID NO:3).

43. A pharmaceutical composition comprising:

a pharmaceutically acceptable excipient; and

a polypeptide having the formula:

$CX^1X^2X^3X^4X^5X^6CX^7X^8X^9X^{10}X^{11}X^{12}CCDPX^{13}ATCYCX^{14}X^{15}X^{16}NAFCYCR_n$

wherein

X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11}, X^{12}, X^{13}, X^{14}, X^{15}, and X^{16} are independently selected amino acids, and

n is zero or one.

44. The composition of claim 43, wherein said polypeptide is not CVRLHESCLGQQVPCCDPAATCYCRFFNAFCYC (SEQ ID NO:3).

45. A method of identifying a compound that modulates ligand binding to a melanocortin receptor, said method comprising: modeling test compounds that fit spatially into a melanocortin receptor ligand binding site of interest using an atomic structural model of a melanocortin receptor binding region or portion thereof; screening said test compounds in an assay characterized by binding of a test compound to a melanocortin receptor ligand binding site; and identifying a test compound that modulates ligand binding to said melanocortin receptor.

46. The method of claim 45, wherein said melanocortin receptor binding region comprises the minimized agouti related protein receptor binding region or portion thereof.

47. The method of claim 45, wherein said atomic structural model comprises atomic coordinates of amino acid residues corresponding to residues 1-18 of the N-terminal loop of the minimized agouti related protein (residues 1-18 of SEQ ID NO:2), residues 19-13 of the central loop of the minimized agouti related protein (residues 19-34 of SEQ ID NO:2), and residues 35-46 of the C-terminal loop of the minimized agouti related protein (residues 35-46 of SEQ ID NO:2).

48. The method of claim 45, wherein said atomic structural model comprises atomic coordinates of amino acid residues corresponding to residues 19-34 of the central loop of the minimized agouti related protein (residues 19-34 of SEQ ID NO:2) and at least residues 15-18 of the N-terminal loop of the minimized agouti related protein (residues 15-18 of SEQ ID NO:2).

49. The method of claim 45, wherein said atomic structural model comprises atomic coordinates of amino acid residues corresponding to residues 19-34 of the central loop of the minimized agouti related protein (residues 19-34 of SEQ ID NO:2) and at least 20% of the contiguous or non-contiguous residues or their atoms are selected from residues 1-18 of the N-terminal loop of the minimized agouti related protein (residues 1-18 of SEQ ID NO:2).

50. The method of claim 45, wherein said atomic structural model comprises atomic coordinates of amino acid residues corresponding to residues 24-31 of the active loop of the minimized agouti related protein (residues 24-31 of SEQ ID NO:2).

51. The method of claim 45, wherein said atomic structural model comprises atomic coordinates of amino acid residues corresponding to residues 25-27 of the active loop of the minimized agouti related protein (residues 25-27 of SEQ ID NO:2).

52. The method of claim 45, wherein said screening is in vitro.

53. The method of claim 52, wherein said screening is high throughput screening.

54. The method of claim 45, wherein said assay is a biological assay.

55. The method of claim 45, wherein said test compound is from a library of compounds.

56. The method of claim 45, wherein said test compound is an agonist or antagonist of ligand binding.

57. The method of claim 56, wherein said test compound is a small organic molecule, a peptide, or peptidomimetic.

58. A method for identifying an agonist or antagonist of ligand binding to a melanocortin receptor, said method comprising the steps of: providing the atomic coordinates of a melanocortin receptor binding region or portion thereof to a computerized modeling system; modeling compounds which match or mimic the receptor binding region and thus fit spatially into the melanocortin receptor ligand binding site; and identifying in an assay for melanocortin receptor activity a compound that increases or decreases the activity of said melanocortin receptor by binding the ligand binding site of said melanocortin receptor, whereby an agonist or antagonist of ligand binding is identified.

59. The method of claim 58, wherein said melanocortin receptor binding region comprises the minimized agouti related protein receptor binding region or portion thereof.

60. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule that binds a melanocortin receptor comprising structure coordinates of amino acid residues corresponding to residues 1-18 of the N-terminal loop of the minimized agouti related protein (residues 1-18 of SEQ ID NO:2), residues 19-13 of the central loop of the minimized agouti related protein (residues 19-34 of SEQ ID NO:2), and

residues 35-46 of the C-terminal loop of the minimized agouti related protein (residues 35-46 of SEQ ID NO:2), or a homologue of said molecule.

61. The machine readable storage medium of claim 60, wherein said molecule is a melanocortin receptor agonist.

62. The machine readable storage medium of claim 60, wherein said molecule is a melanocortin receptor antagonist.

63. The machine-readable data storage medium according to claim 60 herein said molecule is defined by the set of structure coordinates depicted in Table 4 or Table 5, or a homologue of said molecule, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 2.54Å.

64. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data,, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates selected from the group consisting of coordinates depicted in Table 4 or Table 5; and said second set of data comprises an X-ray diffraction pattern of a molecule.

65. An NMR structure of the minimized agouti related protein, embodied in a computer readable media.

66. A polypeptide comprising the amino acid sequence:

CVRLHESCLGQQVPCCDPAATCYCRFFNAFCYC (SEQ ID NO:3)

or a modified form thereof, wherein said polypeptide is not a full-length AGRP and said polypeptide is not a MARP.

67. The polypeptide of claim 66, wherein the polypeptide is chemically synthesized.

68. A method of treating a disease state in mammals that is alleviated by treatment with a polypeptide having an amino acid sequence:

CVRLHESCLGQQVPCCDPAATCYCRFFNAFCYC (SEQ ID NO:3)

which method comprises administering to a mammal in need of such a treatment a therapeutically effective amount of said polypeptide, or a pharmaceutically acceptable salt thereof.

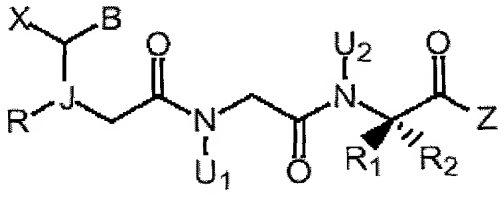
69. The method of claim 68, wherein said disease state is a wasting syndrome.

70. A pharmaceutical composition comprising a therapeutically effective amount of a polypeptide of the sequence:

CVRLHESCLGQQVPCCDPAATCYCRFFNAFCYC (SEQ ID NO:3)

or a pharmaceutically acceptable salt thereof.

71. A non-peptide melanocortin receptor ligand of the structural formula:



wherein

B, U_1, U_2, R, R_1, and R_2 are independently selected from the group consisting of: hydrogen, alkyl, derivatized alkyl, cycloalkyl, derivatized cycloalkyl, halocycloalkyl, aloxycycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

J is selected from the group consisting of carbon, nitrogen, silicon, and sulfur;

X is selected from the group consisting of hydrogen, carbon, nitrogen, oxygen, silicon, and sulfur; and

Z is selected from the group consisting of a continuing peptide bond, a hydroxyl; $-NH_2-$, -NH-(n), and -N-(n,n'), and -O-(y), where where n and n' are independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and a derivatized form thereof, and y is selected from

the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl heteroarylalkyl, and a derivatized form thereof.

72. The non-peptide melanocortin receptor ligand according to claim 71, wherein said ligand is a ligand for a melanocortin receptor selected from the group consisting of MC3r and MC4r.

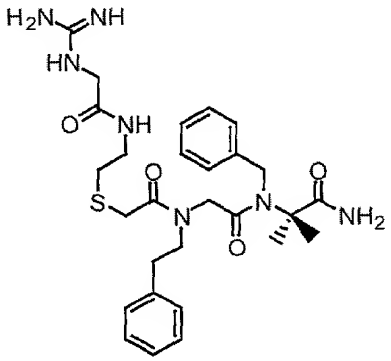
73. The non-peptide melanocortin receptor ligand according to claim 71, wherein said ligand has a molecular weight ranging from about 200 to 1000 daltons.

74. The non-peptide melanocortin receptor ligand according to claim 71, wherein said ligand has a structure that mimics the backbone of the AGRP active loop.

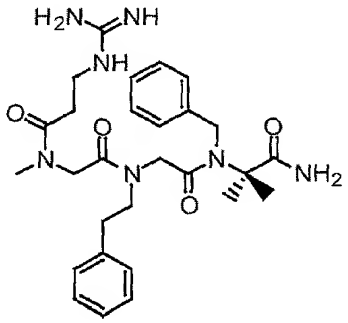
75. The non-peptide melanocortin receptor ligand according to claim 71, wherein said ligand comprises a terminal gaunidino moiety.

76. The non-peptide melanocortin receptor ligand according to claim 71, wherein said ligand comprises at least one methylbenzyl moiety.

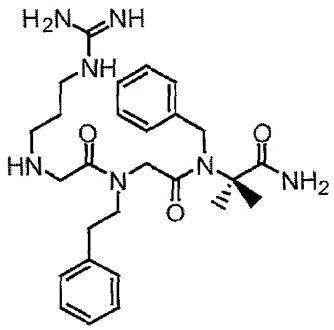
77. The non-peptide melanocortin receptor ligand according to claim 71, wherein said ligand has the structural formula:



78. The non-peptide melanocortin receptor ligand according to claim 71, wherein said ligand has the structural formula:



79. The non-peptide melanocortin receptor ligand according to claim 71, wherein said ligand has the structural formula:



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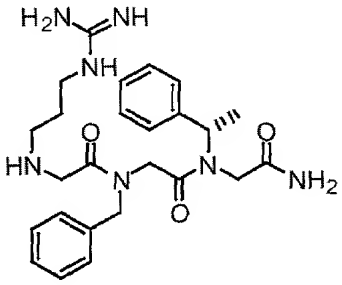
80. The non-peptide melanocortin receptor ligand according to claim 71, wherein said ligand has the structural formula:



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81. A pharmaceutical preparation of a non-peptide melanocortin receptor ligand according to claim 71.

82. The pharmaceutical preparation according to claim 81, wherein said ligand is a melanocortin receptor antagonist.

83. The pharmaceutical preparation according to claim 82, wherein said ligand is a melanocortin receptor agonist.

84. A method for modulating a melanocortin receptor mediated physiological process, said method comprising:

contacting said melanocortin receptor with a non-peptide melanocortin receptor ligand according to claim 71.

85. The method according to claim 84, wherein said ligand is a melanocortin receptor agonist.

86. The method according to claim 84, wherein said ligand is a melanocortin receptor antagonist.